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(71) Applicant: 591032596

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250 Frankfurter Schtrasse, Darmschtatt

D-64293, Germany

(74) Agent: Patent Attorneys, Sei-ji Katsu-wa (and one other)

(54) Patent Title: 4-(Arylaminomethylene)-2,4-dihydro-3-pyrazolone Compounds

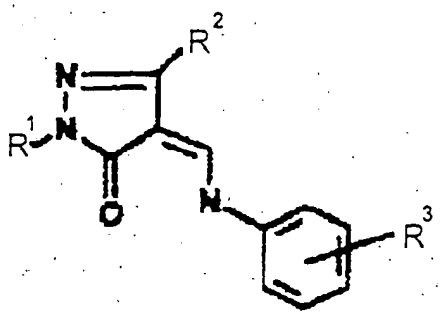
(57) Summary (Amendment exists.)

Purpose:

To find compounds having useful pharmacological activities.

Means to Resolution:

It has been found that 5-Pyrazolinone derivatives, expressed by formula (I), and pharmacologically acceptable salts thereof, can be used as a selectively inhibitory medicine against cGMP-specific phosphodiesterase (cGMP PDE):



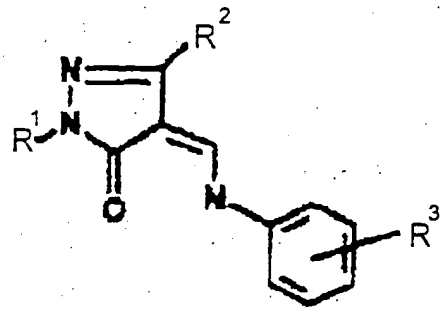
(I)

[wherein, in the formula, R^1 represents benzyl, phenyl, phenyl having 1 ~ 3 substituents of amino, halogeno, NO_2, CN, acyl, AO-, N,N-dialkylcarbamoyl, A-O-CO-NH-, $SO_2NR^4R^5$(in this group, R^4 and R^5 are H, C_1 ~C_6 alkyl and so forth), tetrazolyl, phospho and so forth, or pyridyl; R^2 represents C_1 ~ C_5 alkyl, alkoxycarbonyl-C_1 ~ C_5 alkyl and so forth; R^3 represents H, C_1 ~ C_5 alkyl and so forth; and A represents C_1 ~ C_6 alkyl (which may be substituted by fluorine or chlorine).] The production method of these compounds has been established and these compounds are used as pharmacologically active materials.

What is claimed is:

Claim 1

Compounds expressed by formula (I) below, and salts thereof:



(I)

wherein, in the formula, R^1 represents a benzyl, an alkoxybenzyl whose alkyl section has 1 ~ 3 C atoms, a phenyl, a phenyl having 1 ~ 3 substituents of amino, cyano, halogeno, nitro, A-CO-, carboxy, AO-, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl (whose alkyl section has 1 ~ 6 C atoms), A-O-CO-, A-O-CO-NH-, A-O-CO-NA-, A-CO-NH-, A-CO-NA-, HSO_3-, A-SO_2-, $SO_2NR^4R^5$(in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)), A-CO-NH-SO_2-, A-CO-NA-SO_2-, A-SO_2-NH-, A-SO_2-NA-, (A-SO_2-)$_2$N-, tetrazolyl, or phospho, or a pyridyl; R^2 represents an alkyl having 1 ~ 5 C atoms, an alkoxycarbonylalkyl, a hydroxyalkyl, or a hydroxycarbonylalkyl; R^3 represents a H, a straight or branched alkyl having 1 ~ 5 C atoms, a straight or branched alkoxy having 1 ~ 5 C atoms, an alkyl substituted with fluorine or chlorine, aminoalkyl, aminoalkanoyl or sulfamoyl (which is expressed by $SO_2NR^4R^5$, wherein in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)); and A represents a straight or branched alkyl having 1 ~ 6 C atoms, or a straight or branched alkyl which has 1 ~ 6 C atoms and which is substituted by fluorine or chlorine.

Claim 2

Compounds expressed by formula (I) described in Claim 1, and salts thereof,

wherein, in the formula, R^1 represents a benzyl, an alkoxybenzyl whose alkyl section has 1 ~ 3 C atoms, a phenyl, a phenyl having 1 ~ 3 substituents of amino, halogeno, nitro, HSO_3-, cyano,

carboxyl, A-O-CO-, A-CO-NH-, A-CO-NA-, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl (whose alkyl section has 1 ~ 6 C atoms), A-SO_2-NH-, A-SO_2-NA-, $SO_2NR^4R^5$(in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)), A-CO-NH-SO_2-, A-CO-NA-SO_2-, acylsulfonamide, tetrazolyl, or phospho, or a pyridyl; R^2 represents a hydroxyalkyl; R^3 represents a H, a straight or branched alkyl having 1 ~ 5 C atoms, a straight or branched alkoxy having 1 ~ 5 C atoms, or an alkyl substituted with fluorine or chlorine; and A is the same as that defined in Claim 1.

Claim 3

Compounds expressed by formula (I) described in Claim 1, and salts thereof,

wherein, in the formula, R^1 represents a benzyl, an alkoxybenzyl whose alkyl section has 1 ~ 3 C atoms, a phenyl, a phenyl having 1 ~ 3 substituents of A-CO-NH-, A-CO-NA-, N-alkylcarbamoyl, N,N-dialkylcarbamoyl (whose alkyl section has 1 ~ 6 C atoms), A-CO-NH-SO_2-, A-CO-NA-SO_2-, HSO_3-, $SO_2NR^4R^5$(in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)), tetrazolyl, or phosphonyl, or a pyridyl; R^2 represents H_3C-O-CO-CH_2-; R^3 represents an aminoalkyl, an aminoaklanoyl or $SO_2NR^4R^5$, (wherein in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)); and A is the same as that defined in Claim 1.

Claim 4

Methyl N-(3-(4(-2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)carbamate; 4-((2-ethoxyanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)-N-ethylbenzenesulfonamide; ethyl 2-(1-(4-(N,N-diethylsulfamoyl)phenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-(N,N-diethylsulfamoyl)phenyl)-4-(2-ethoxyanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1-(4-trifluoroacetoamidophenyl)-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-ethoxycarbonylaminophenyl)-4-(2-ethylanilinomethylene)-4,5-

dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methanesulfonamidephenyl)-5-oxo-1H-pyrazole-3-yl)acetate; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-5H-pyrazole-1-yl)phenyl)acetoamide; N,N-diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; N-ethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; 4-(2-ethoxyanilinomethylene)-2,4-dihydro-5-methyl-2-(4-(4-morpholinylsulfonyl)phenyl)-3H-pyrazole-3-one; 4-(2-ethylanilinomethylene)-2,4-dihydro-5-methyl-2-(4-(4-methyl-1-piperazinylsulfonyl)phenyl)-3H-pyrazole-3-one; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)methanesulfonamide; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-5-yl)phenyl)trifluoroacetoamide; N-(4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)-N-methylsulfonylmethanesulfonamide; N,N-diethyl-4-(4,5-dihydro-4-(2-ethoxyanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; N,N-diethyl-4-(4,5-dihydro-4-(2-methoxyanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; 3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzenesulfonic acid; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzenesulfonic acid; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-nitrophenyl)-5-oxo-1H-pyrazole-3-yl)acetate; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)-N-hexylbenzamide; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzamide; N,N-diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzamide; 4-(2-ethylanilinomethylene)-2,4-dihydro-5-propyl-2-(4-pyridyl)-3H-pyrazole-3-one; N,N-diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzamide; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)-N-hexylbenzamide; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzamide; 4-(2-ethylanilinomethylene)-2,4-dihydro-5-propyl-2-(4-(1H-tetrazole-5-yl)phenyl)-3H-pyrazole-3-one; 4-(2-ethylanilinomethylene)-2,4-dihydro-5-methyl-2-(3-(1H-tetrazole-5-yl)phenyl)-3H-pyrazole-3-one; 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-trifluoromethylanilinomethylene)-1H-pyrazole-1-yl)benzoic acid; 4-(4-(2-ethylanilinomethylene)-3-ethoxycarbonylmethyl-4,5-dihydro-5-oxo-1H-pyrazole-1-yl)benzoic acid; 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-(2-propionyloxy)anilinomethylene)-1H-pyrazole-1-yl)benzoic acid; 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-propoxyanilinomethylene)-1H-pyrazole-1-

yl)benzoic acid; 4-(4,5-dihydro-4-(2-isopropylanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid; 3-(4-(2-ethylanilinomethyleneaminomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-trifluoroacetoamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-methoxycarbonylaminophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methanesulfonamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-(N,N-diethylsulfamoyl)phenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-(N,N-diethylsulfamoyl)phenyl)-4-(2-ethoxyanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1-(4-trifluoroacetoamidophenyl)-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methoxycarbonylaminophenyl)-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methanesulfonamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methoxycarbonylaminophenyl)-5-oxo-1H-pyrazole-3-yl)acetic acid; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)methanesulfonamide; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)acetoamide; methyl N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)carbamate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1-(3-trifluoroacetoamidophenyl)-1H-pyrazole-1-yl)acetate; and ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(3-methanesulfonamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate

Claim 5

Compounds expressed by formula (I) described in Claim 1, and salts thereof,

wherein, in the formula, R^1 represents a benzyl, an alkoxybenzyl whose alkyl section has 1 ~ 3 C atoms, a phenyl, a phenyl having 1 ~ 3 substituents of amino, halogeno, nitro, HSO_3-, cyano, carboxyl, A-O-CO-, A-CO-NH-, A-CO-NA-, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl (whose alkyl section has 1 ~ 6 C atoms), A-SO_2-NH-, A-SO_2-NA-, $SO_2NR^4R^5$(in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may

include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)), A-CO-NH-SO_2-, A-CO-NA-SO_2-, acylsulfonamide, tetrazolyl, or phospho, or a pyridyl; R^2 represents an alkyl having 1 ~ 5 C atoms, an alkoxycarbonylalkyl, a hydroxyalkyl, or a hydroxycarbonylalkyl; R^3 represents a H, a straight or branched alkyl having 1 ~ 5 C atoms, a straight or branched alkoxy having 1 ~ 5 C atoms, an alkyl substituted with fluorine or chlorine, aminoalkanoyl, aminoalkyl, or $SO_2NR^4R^5$ (wherein in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O).

Claim 6

Usage of medicines described in Claim 5 as a selective inhibitory medicine against cGMP-specific phosphodiesterase.

Claim 7

Usage of the compounds which are described in Claim 5 or pharmacologically acceptable salts of said compounds in production of pharmaceuticals.

Claim 8

Usage of the medicines which are described in Claim 5 to treat pathological conditions.

Claim 9

Application of the medicines described in Claim 5 for the production of pharmaceuticals to treat angio cardiopathy and cardiac failure.

Claim 10

Pharmaceuticals which include at least one of the compounds described in Claims 1 ~ 4 and(or) at least one of the physiological salts thereof, or medicines described in Claim 5.

Claim 11

Pharmaceuticals which include at least one of the medicines described in Claim 5 and which are in an appropriate medicinal form together with a liquid or pseudo liquid solvent or auxiliary agent.

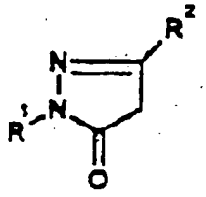
Claim 12

Production method of the compounds which are described in Claims 1 ~ 4, or the medicines which are described in Claim 5,

wherein

a compound, which is expressed by a general formula II,

[Chemical 2]

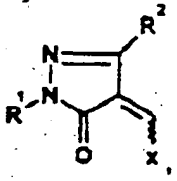


(II)

is reacted with a formaldehyde-providing compound from a group of triazine, dimethylformamide, dimethylformamidedimethylacetal, Gold's reagent, formylchloride, formamide or alkyl derivatives of formamide whose alkyl section has 1 ~ 6 C atoms, or a formaldehyde-providing compound from a group of trialkylorthoformates, but preferably with trimethylorthoformate, wherein R1 and R2 have the definitions described in Claims 1 ~ 3 or Claim 5;

a compound, which is expressed by a general formula IIa, is generated,

[Chemical 3]



(IIa)

wherein X is an amino, or O-alkyl group (whose alkyl section has 1 ~ 6 C atoms);

subsequently or in some cases, right there and then, this compound is reacted with an appropriate aniline derivative, which is expressed by a formula III, or a salt thereof,

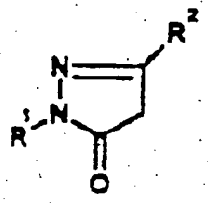
Claim 12

Production method of the compounds which are described in Claims 1 ~ 4, or the medicines which are described in Claim 5,

wherein

a compound, which is expressed by a general formula II,

[Chemical 2]

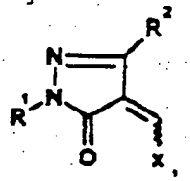


(II)

is reacted with a formaldehyde-providing compound from a group of triazine, dimethylformamide, dimethylformamidedimethylacetal, Gold's reagent, formylchloride, formamide or alkyl derivatives of formamide whose alkyl section has 1 ~ 6 C atoms, or a formaldehyde-providing compound from a group of trialkylorthoformates, but preferably with trimethylorthoformate, wherein R1 and R2 have the definitions described in Claims 1 ~ 3 or Claim 5;

a compound, which is expressed by a general formula IIa, is generated,

[Chemical 3]

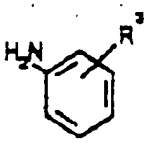


(IIa)

wherein X is an amino, or O-alkyl group (whose alkyl section has 1 ~ 6 C atoms);

subsequently or in some cases, right there and then, this compound is reacted with an appropriate aniline derivative, which is expressed by a formula III, or a salt thereof,

[Chemical 4]



(III)

so that the compound, which is expressed by formula I, is generated, wherein R^3 is defined as is described in Claims 1 ~ 3 or Claim 5;

and(or) one or more groups in the compound, which is expressed by formula I, are changed to one or more different groups;

or the compound, which is expressed by formula II, is reacted with arylisocyanate under the presence of a base from a group of butyllithium and methyllithium.

Detailed Explanation of Invention

[0001]

Technical Field of Invention

The present invention relates to new 5-pyrazolinone derivatives and physiologically acceptable salts thereof, production methods of these compounds, usage of these compounds as medicines, in particular the usage as a selective inhibitory medicine against cGMP-specific phosphodiesterase (cGPM PDE), and pharmaceuticals having these compounds as their active materials.

[0002]

Prior Technology

Numerous compounds having inhibitory effects against cGMP PD esterases have been published. For example, EP-A1-0201188 describes pyrazolo[4,3-d]pyrimidine-7-one as an adenosine-receptor antagonist and as a PDE-inhibitory medicine, which can be used for treating cardio coronary angiopathy associated with cardiac failure or dysfunction. However, this publication does not disclose

concrete examples of these compounds. Nor does it disclose that these compounds have the effects as PDE inhibitors and in particular specific effects against cGMP PDE.

[0003]

WO-A1 93/06104 discloses substituted pyrazolo[4,3-d]pyrimidine-7 one compounds having cGMP PD esterase-specific inhibitory effects, which are improved compared to the compounds described in the previous publication. However, this publication does not disclose the selectivity of these compounds against other phosphodiesterases I, II and III. Nonetheless, simultaneous suppression effects of the compounds against these different phosphodiesterases are particularly important. The reason is that when these compounds are used as medicines, the simultaneous suppression effects against other esterases other than cGMP phosphodiesterase (PDE V) create generally undesirable side effects.

[0004]

Issues to be Resolved by the Present Invention

The purpose of the present invention is to find new compounds which can be used for production of medicines. Another purpose of the present invention is to find compounds which show remarkable suppression effects against cGMP phosphodiesterase (PDE V), and which show no, or little if any, simultaneous suppression effects against other kinds of phosphodiesterases so that the compounds do not exhibit notable side effects which are caused by the suppression of PD esterases I ~ IV.

[0005]

At the same time, another purpose of the present invention is to provide a method to produce the corresponding compounds with as high a purity and with as high a yield as possible. Yet another purpose of the present invention is to find compounds which exhibit particularly remarkable suppression effects against platelet agglutination.

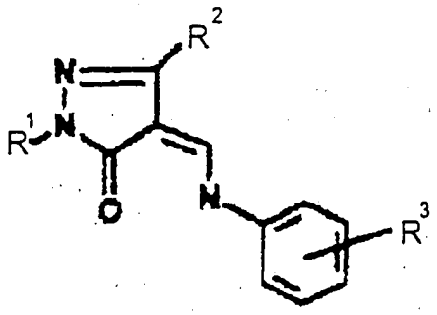
[0006]

Disclosure of Method to Resolve the Issues and Disclosure of the Present Invention

The present invention has found that 5-pyrazolinone derivatives, which are expressed by formula I below, and physiologically acceptable salts thereof are useful in solving the above issues.

[0007]

[Chemical 5]



(I)

[0008]

In the formula, R^1 represents a benzyl, an alkoxybenzyl whose alkyl section has 1 ~ 3 C atoms, a phenyl, a phenyl having 1 ~ 3 substituents of amino, halogeno, NO_2, CN, acyl, AO-, HSO_3-, CO_2H, A-O-CO-, A-CO-NH-, A-CO-NA-, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl (whose alkyl section has 1 ~ 6 C atoms), A-O-CO-NH-, A-O-CO-NA-, $SO_2NR^4R^5$(in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)), A-CO-NH-SO_2-, A-CO-NA-SO_2-, A-SO_2-NH-, A-SO_2-NA-, (A-SO_2-)$_2$N-, tetrazolyl, or phospho, or a pyridyl;

[0009]

R^2 represents an alkyl having 1 ~ 5 C atoms, an alkoxycarbonylalkyl, a hydroxyalkyl, or a hydroxycarbonylalkyl; R^3 represents a H, a straight or branched alkyl having 1 ~ 5 C atoms, a straight or branched alkoxy having 1 ~ 5 C atoms, an alkyl substituted with fluorine or chlorine, aminoalkanoyl, aminoalkyl, carbamoyl, or $SO_2NR^4R^5$ (which is expressed by $SO_2NR^4R^5$, wherein in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)); and

[0010]

A represents a straight or branched alkyl having 1 ~ 6 C atoms, or a straight or branched alkyl which has 1 ~ 6 C atoms and which is substituted by fluorine or chlorine. Accordingly, the present invention pertains to the 5-pyrazolinone derivatives, which are expressed by formula I above, and physiologically acceptable salts thereof.

[0011]

The present invention also includes the production methods of these compounds. In particular, the present invention includes the usage of these compounds as a selective inhibitor of cGMP-specific phosphodiesterase (cGMP PDE), and accordingly, their usage as medicinally active compounds.

[0012]

Some of these compounds are publicly known for different purposes and are active as a cGMP PDE inhibitory medicine. These compounds can be utilized for treatments in various medical fields. Nonetheless, these compounds can be particularly utilized for treating diseases which are caused by arterial sclerosis and other cardio coronary angiopathy.

[0013]

The present invention also pertains to new compounds or salts thereof, which correspond to the compounds of formula (I), wherein in the formula, R^1 is phenyl, or phenyl having 1 ~ 3 substituents of halogeno, nitro, cyano, carboxy, or amino; R^2 is a hydroxyalkyl; and R^3 is a H, a straight or branched alkyl having 1 ~ 5 C atoms, a straight or branched alkoxy having 1 ~ 5 C atoms, or an alkyl which is substituted with fluorine or chlorine.

[0014]

Preferred compounds are those which are expressed by the general formula (I) or salts thereof, wherein R^1 has the aforementioned meaning; R^2 is H_5C_2-O-CO-CH_2-; R^3 is an aminoalkanoyl, an alkanoylamino, carbamoyl, or $SO_2NR^4R^5$(in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)).

[0015]

The present invention, in particular, pertains to the following compounds and physiologically acceptable salts thereof: Methyl N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)carbamate; 4-((2-ethoxyanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)-N-ethylbenzenesulfonamide; ethyl 2-(1-(4-(N,N-diethylsulfamoyl)phenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-(N,N-diethylsulfamoyl)phenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate;

[0016]

ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1-(4-trifluoroacetoamidophenyl)-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-ethoxycarbonylaminophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methanesulfonamidephenyl)-5-oxo-1H-pyrazole-3-yl)acetate;

[0017]

N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-5H-pyrazole-1-yl)phenyl)acetoamide; N,N-diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; N-ethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; 4-(2-ethoxyanilinomethylene)-2,4-dihydro-5-methyl-2-(4-(4-morpholinylsulfonyl)phenyl)-3H-pyrazole-3-one;

[0018]

4-(2-ethylanilinomethylene)-2,4-dihydro-5-methyl-2-(4-(4-methyl-1-piperazinylsulfonyl)phenyl)-3H-pyrazole-3-one; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)methanesulfonamide; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-5-yl)phenyl)trifluoroacetoamide; N-(4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)-N-methylsulfonylmethanesulfonamide;

[0019]

N,N-diethyl-4-(4,5-dihydro-4-(2-ethoxyanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; N,N-diethyl-4-(4,5-dihydro-4-(2-methoxyanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; 3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzenesulfonic acid; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzenesulfonic acid;

[0020]

ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-nitrophenyl)-5-oxo-1H-pyrazole-3-yl)acetate; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)-N-hexylbenzamide; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzamide; N,N-diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzamide;

[0021]

4-(2-ethylanilinomethylene)-2,4-dihydro-5-propyl-2-(4-pyridyl)-3H-pyrazole-3-one; N,N-diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzamide; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)-N-hexylbenzamide; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzamide; 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid;

[0022]

4-(2-ethylanilinomethylene)-2,4-dihydro-5-propyl-2-(4-(1H-tetrazole-5-yl)phenyl-3H-pyrazole-3-one; 4-(2-ethylanilinomethylene)-2,4-dihydro-5-methyl-2-(3-(1H-tetrazole-5-yl)phenyl)-3H-pyrazole-3-one; 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-trifluoromethylanilinomethylene)-1H-pyrazole-1-yl)benzoic acid; 4-(4-(2-ethylanilinomethylene)-3-ethoxycarbonylmethyl-4,5-dihydro-5-oxo-1H-pyrazole-1-yl)benzoic acid; 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-(2-propionyloxy)anilinomethylene)-1H-pyrazole-1-yl)benzoic acid;

[0023]

4-(4,5-dihydro-3-methyl-5-oxo-4-(2-propoxyanilinomethylene)-1H-pyrazole-1-yl)benzoic acid; 4-(4,5-dihydro-4-(2-isopropylanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid; 3-(4-(2-ethylanilinomethyleneaminomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide; ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-trifluoroacetoamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate;

[0024]

ethyl 2-(1-(4-methoxycarbonylaminophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methanesulfonamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-(N,N-diethylsulfamoyl)phenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(1-(4-(N,N-diethylsulfamoyl)phenyl)-4-(2-ethoxyanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate;

[0025]

ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1-(4-trifluoroacetoamidophenyl)-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methoxycarbonylaminophenyl)-5-oxo-1H-pyrazole-3-yl)acetate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methanesulfonamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate;

[0026]

ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate; 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methoxycarbonylaminophenyl)-5-oxo-1H-pyrazole-3-yl)acetic acid; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)methanesulfonamide; N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)acetoamide;

[0027]

methyl N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)carbamate; ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1-(3-trifluoroacetoamidophenyl)-1H-pyrazole-1-yl)acetate; and ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(3-methanesulfonamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate.

[0028]

The present invention particularly relates to the compounds, which are expressed by the general formula I, and physiologically acceptable salts thereof, wherein in the formula, R^1 represents a benzyl, an alkoxybenzyl whose alkyl section has 1 ~ 3 C atoms, a phenyl, a phenyl having 1 ~ 3 substituents of amino, halogeno, NO_2, CN, acyl, AO-, HSO_3-, CO_2H, A-O-CO-, A-CO-NH-, A-CO-NA-, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl (whose alkyl section has 1 ~ 6 C atoms), A-O-CO-NH-, A-O-CO-NA-, $SO_2NR^4R^5$(in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)), A-CO-NH-SO_2-, A-CO-NA-SO_2-, A-SO_2-NH-, A-SO_2-NH-, A-SO_2-NA-, (A-SO_2-)$_2$N-, tetrazolyl, or phospho, or a pyridyl;

[0029]

R^2 represents an alkyl having 1 ~ 5 C atoms, an alkoxycarbonylalkyl, a hydroxyalkyl, or a hydroxycarbonylalkyl; R^3 represents a H, a straight or branched alkyl having 1 ~ 5 C atoms, a straight or branched alkoxy having 1 ~ 5 C atoms, an alkyl substituted with fluorine or chlorine, aminoalkanoyl, aminoalkyl, or $SO_2NR^4R^5$ (which is expressed by $SO_2NR^4R^5$, wherein in this group, R^4 and R^5 are a H, or an alkyl having 1 ~ 6 C atoms; or NR^4R^5 may be a 5-member or 6-member ring which may include other hetero atoms, such as N, S or O, and/or an A('s) as a substituent(s)).

[0030]

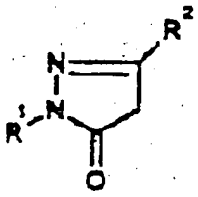
Part of the present invention also includes the usage of medicines as a selective inhibitor of cGMP-specific phosphodiesterase, and accordingly, their usage as medicinally active compounds. Particular forms of the present invention also include the usage of the compounds, which are expressed by the above general formula (I), and(or) corresponding physiologically acceptable salts thereof, or the aforementioned medicines to treat pathological conditions, in particular to treat angio cardiopathy and cardiac failure. In addition, particular forms of the present invention also include pharmaceuticals.

which contain at least one of the compounds, which are expressed by the above general formula (I), and(or) at least one of the corresponding physiologically acceptable salts thereof, or at least one of the corresponding medicines. However, the present invention further pertains to pharmaceuticals, which contain at least one of the compounds, which are expressed by the above general formula (I), (wherein in the formula, R^1, R^2 and R^3 have the same definitions as previously described,) and(or) at least one of the corresponding physiologically acceptable salts thereof, or at least one of the corresponding medicines, wherein such pharmaceuticals are mixed with at least one solid, liquid or pseudo liquid solvent or auxiliary agent and are in an appropriate medicinal form.

[0031]

The present invention, moreover, includes the production methods of the compounds, which are expressed by the aforementioned formula (I) containing the substituents, R^1, R^2 and R^3 as defined hereinabove, or the production methods of corresponding inhibitory medicines. In such production methods, a compound, which is expressed by a general formula II,

[Chemical 6]



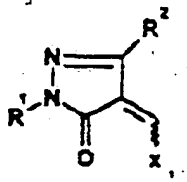
(II)

is reacted with an appropriate formaldehyde-providing compounds such as triazine or trialkylorthoformate, in particular with trimethylorthoformate, wherein R1 and R2 are defined as previously described;

[0032]

a compound, which is expressed by a general formula IIa, is generated,

[Chemical 7]



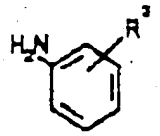
(IIa)

wherein X is an amino, or O-alkyl group (whose alkyl section has 1 ~ 6 C atoms);

subsequently or in some cases, right there and then, this compound is reacted with an appropriate aniline derivative, which is expressed by a formula III, or a salt thereof,

[0033]

[Chemical 8]



(III)

so that the compound, which is expressed by formula I, is generated, wherein R^3 is defined as previously described;

and(or) one or more groups R in the compound, which is expressed by formula I, are changed to one or more different groups R.

[0034]

The compounds, which are expressed by formula (I) and which contain mostly different substituents, are described as herbicides and as fungicides in the Patent Application EP-B1 0274642. Accordingly, it is surprising that the compounds, which are expressed by the general formula (I), functions as a selective inhibitory medicine against c-GMP-specific phosphodiesterase, and can be used to treat angio cardiopathy and cardiac failure. A particular advantage in using the compounds of the present invention as medicinally active materials lies in the fact that these compounds very specifically suppress cGMP phosphodiesterase (PDE V), but conversely their measurable suppression effects against phosphodiesterases, PDE's I, II, III and IV, are one ten-thousandth. In other words, measurable suppression effects against phosphodiesterases, PDE's I, II, III and IV, are negligible. Thence, the usage of compounds, having such specific effects, as medicines eliminate side effects, which normally accompany suppression of other phosphodiesterases.

[0035]

The compounds, which are expressed by formula II, and their source materials can be produced by the methods, which are disclosed in the numerous publications by those who are skilled in the art, or by slightly modified methods thereof. For example, appropriate methods are described in the patent, EP-B1 0274642, or in standard technical books such as "Methoden der Organischen Chemie" by Houben-Weyl, Georg-Theime Publisher, Stuttgart. A second example is an overview by R. H. Wiley, and P. Wiley called "Pyrazolones, Pyrazolidones, and Derivatives", Interscience Publishers, John Wiley & Sons (1964). They are also described in the following publications:

[0036]

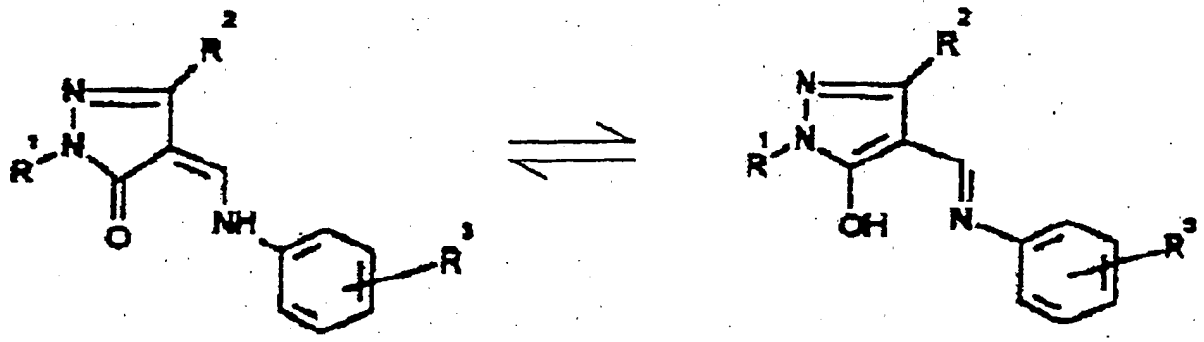
C. Ringel, R. Mayer, and J. Prakt, Chem. 26(1964), pages following p333; J. F. Gillespie, and C. C. Price, J. Org. Chem. 22 (1957), pages following p780; K. Tabel, E. Kawashima, and T. Kato, Chem. Pharm. Bull (CPBTAL), 29 (1) (1981), pages following p244; J. D. Wilson, T. D. Fulmer, L. B. Dasher, and C. F. Beam, J. Heterocycl. Chem., 17 (2) (1980), pp389~391; H. Neunhoefer, G. Koehler, and H. J. Degen, Liebigs Ann. Chem. (1985), N1, pp78~89; S. Ege, A. D. Adams, E. J. Gess, K. S. Ragone, and B. J. Kober, J. Chem. Soc., Perkin Trans. (1983) N2, pages following p325; R. B. Pathak, and S. C. Bahel, J. Indian Chem. Soc. 57 (1980) pp1108 ~ 1111; M. I. Ali, M. M. S. EI-Morsy, H. A. Hammouda and M. F. Sharaf, Egypt. J. Chem. 22 (1979), pp179 ~ 188; and F. J. Mcevoy and J. D. Albright, J. Org. Chem., 44 (1979), pp4597 ~ 4603.

[0037]

In the subsequent reaction process, the compounds, which are expressed by formula II, are reacted further and the compounds, which are expressed by formula I, are generated. The obtained material may be geometrical isomers or a mixture of isomers with various compositions. The reaction can take place through an intermediate product, in which the 4th substitution site of said pyrazoline ring is substituted by a methylene group. Alternatively, a subsequent reaction with an aniline derivative or a substitution reaction can be directly performed using a corresponding aniline derivative. In such a case, the choice of change in the production method is influenced by the chemical characteristics of the substituent of said pyrazoline compound. Part of the compound of formula I, which is being produced, can exist under a tautomer equilibrium:

[0038]

[Chemical 9]

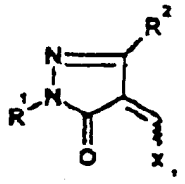


Herein, the terminology usage regarding the compounds expressed by formula I means both pure compounds and a mixture of tautomers or isomers of various ratios.

[0039]

In particular, both new compounds and compounds, which had been disclosed heretofore, can be produced by reacting a compound, which is expressed by a general formula IIa, with an appropriate aniline derivative, which is expressed by a general formula III,

[Chemical 10]

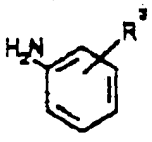


(IIa)

wherein R1 and R2 are defined as previously described, and X can be an amino group, or an alkoxy group,

[0040]

[Chemical 11]



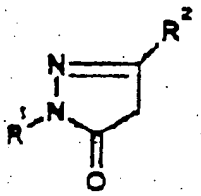
(III)

and wherein R^3 is defined as previously described. This reaction is performed at a temperature of 0 ~ 120 degrees Celsius, in particular at a raised temperature and in some cases, under the presence of an appropriate diluting agent.

[0041]

The compound, which is expressed by formula IIa, can be produced by reacting an appropriate compound, which is expressed by formula II,

[Chemical 12]



(II)

with a formaldehyde-providing compound from a group of triazine, dimethylformamide, dimethylformamidedimethylacetal, Gold's reagent, formylchloride, formamide or alkyl derivatives of formamide whose alkyl section has 1 ~ 6 C atoms, or a formaldehyde-providing compound from a group of trialkylorthoformates, preferably with trimethylorthoformate.

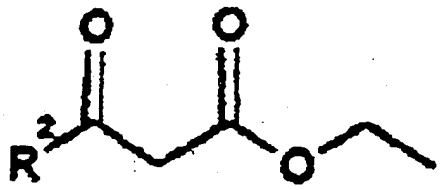
[0042]

As necessary, this reaction is carried out in an appropriate diluting agent, which does not interfere with the subsequent reactions, such as glacial acetic acid. If possible, the reaction should take place under the presence of an appropriate catalyst. The compounds, which are expressed by formula IIa, can be isolated as intermediate products. However, these compounds can be reacted with corresponding amine compounds, which are expressed by formula III, right there and then, and further reactions can directly take place. Then, the compounds, which are expressed by formula I, are generated. Another synthesis path of the compounds, which are expressed by formula I, is particularly desirable if the compounds, which are expressed by formula II, have reaction sensitive substituents with respect to the reaction with a formaldehyde-providing compound, or the reaction with an aniline derivative, which is expressed by formula III. In these cases, it is preferred to react the corresponding arylisocyanates with the corresponding compounds, which are expressed by formula II, under the presence of a base, in particular butyllithium or methyllithium, using a publicly known method.

[0043]

The compounds, which are expressed by the general formula II, are normally produced, by reacting a b-keto-ester compound or a 1,3-dicarbonyl compound, both of which are expressed by a general formula IV below, with a hydrazine compound, which is expressed by a general formula V, or a salt thereof, such as a hydrochloride thereof, a hydrogensulfate thereof and a oxalate thereof,

[Chemical 13]



(IV)

wherein R^2 is defined as above,

[Chemical 14]

(V)

and wherein the reaction is performed under the presence of an appropriate diluting agent as necessary, which does not interfere with the subsequent reactions of the reaction product, such as ethanol. Further, if necessary, the reaction is performed under the of an appropriate catalyst, such as toluenesulfonic acid.

[0044]

The 1,3-dicarbonyl compound to be used hereinabove, which is expressed by formula IV, is in general, a publicly known compound in organic chemistry. It is commercially sold or can be synthesized using a method which is known to those skilled in the art. The hydrazine compound, which is necessary for performing the cyclization reaction, is a publicly known compound or can be obtained using a method which is known to those skilled in the art. (e.g., cf. "Methoden der Organischen Chemie, vol. x" by Houben-Weyl, p2.203, Georg-Theime Publisher, Stuttgart)

[0045]

As previously described, the compounds of the present invention have more than average selectivity as a cGMP PD esterase inhibitory medicine. In other words, the effects of these inhibitors increase the concentration of cGMP in a human body. The effects thereof are the useful increase in platelet agglutination suppression, increase in granulocyte activities, increase in vasospasm activities and vasodilatation activities, and the enhancement of the endothelium-derived relaxing factor effects. Accordingly, these compounds can be utilized in order to treat various pathological conditions, including hypertension of various severity, cardiac failure of various causes, arterial sclerosis, disorders which result from narrowed blood vessels, such as apoplexy, bronchitis, chronic and allergic asthma, allergic hay fever, glaucoma, and disorders characterized by dysfunction of digestive system movements.

[0046]

The biological activities of the compounds of the present invention can be proved, for example, by the same method as that described in the international patent application, WO-A1-93/06104. In other words, the affinity of the compounds to cGMP phosphodiesterase and cAMP phosphodiesterase can be determined by measuring their IC_{50} value (the inhibitor concentration which is necessary to suppress 50% of the enzyme activity). This measurement was carried out using enzymes, which were isolated using a publicly known method (e.g., the method described in W.J. Thompson, et. al., Biochem., 1971, 10, 311). This test was carried out using a variation of the batch method by W. J. Thompson and M. M. Appleman (Biochem., 1979, 18, 5228).

[0047]

The test results proved that the compounds, which are expressed by the general formula I, are effective and selective inhibitory medicines against cGMP phosphodiesterase. This is particularly so with the compounds whose R^1 is benzoic acid, benzenesulfonic acid, N-methyl- or N,N-dialkylbenzenesulfonic acid, acylaminophenyl, N,N-diethylbenzamide or benzamide. Furthermore, the compounds of the general formula I, having a substituent of methyl or propyl as R^1 and a substituent of benzoic acid, benzamide, N-hexylbenzamide or N,N-diethylbenzamide, benzenesulfonamide, or acylaminophenyl as R^2, show particularly notable platelet agglutination suppression effects.

[0048]

Therefore, the compounds, which are expressed by the general formula I, and physiologically acceptable salts thereof are combined with at least one solvent or auxiliary agent and, when desired, with one or more other active materials and thus, can be used for production of pharmaceuticals. The pharmaceuticals, which are obtained this way, can be used as medicines for medical treatment of humans or animals. An appropriate carrier material should be suitable for enteral application (e.g., peroral or per rectum) or parenteral application, or an application in a form of inhalation spray. In addition, an appropriate carrier material is an organic or inorganic material which shall not react with the new compounds of the present invention. Examples of such an appropriate carrier material include water, vegetable oil, benzylalcohol, polyethyleneglycol, glyceroltriacetate and other alipatic acids, glycerides, gelatin, soya lecithin, hydrocarbons (such as lactose or starch), magnesium stearate, talc, or cellulose.

[0049]

Tablets, coated tablets, capsules, syrup, liquid, or drips are particularly suitable for peroral applications. Coated tablets with a coating, which is resilient against gastric juice, and capsules with a shell, which is resilient against gastric juice, are especially important. For applying per rectum, a suppository is used. As for a parenteral application, a solution, preferably an oily or aqueous solution or suspension, emulsion or an implant is used. When inhalation spray is used for application, a spray solution, which includes active materials dissolved or suspended in a mixture with a spray gas, such as chlorofluorocarbon, is used. In this case, active materials are preferably in a fine particulate form. Moreover, one or more additional physiologically tolerated solvents, such as ethanol, can exist. An inhalation solution can be given using an ordinary inhalation tool. The active materials of the present invention can also be freeze-dried. The obtained freeze-dried materials can be used, for example, to produce injection solutions.

[0050]

The above pharmaceuticals can be sterilized and/or include an auxiliary agent, a preservative, a stabilizing agent and/or a humectant, emulsifier, salts to influence the osmotic pressure, a buffer material, a colorant, and/or a flavoring additive. When desired, these pharmaceuticals can also include

one or more other active materials, vitamins, diuretics, and antiphlogistics. The compounds, which are expressed by formula I of the present invention, can be generally applied in the same manner as other publicly known commercial medicines. In particular, they can be applied in the same manner as the compounds described in US-A 4880804. Preferably, approximately 1mg ~ 1g, and more preferably 50 ~ 500mg is applied per unit dose. The daily dosage amount is preferably 0.1 ~ 50mg/body weight in kg, and more preferably 1 ~ 10mg/boyd weight in kg. Nonetheless, a specific dosage for each patient depends on a very wide range of factors, such as the activities of the specific compounds under use, patient's age, weight, general health conditions, gender, food, timing and method of the dose, the rate of excretion, the combination of employed medications, and the severity of the specific pathological conditions. A peroral application is preferred.

[0051]

Embodiments

Examples hereinbelow are intended for the explanation purpose of the present invention. They are not meant to restrict the present invention. In the examples below, the terminology, an "ordinary finishing process", means the following: As necessary, water is added. Depending on the necessity stemming from the structure of the final product, its pH is adjusted to 2 ~ 10. Extraction is performed using ethyl acetate or dichloromethane. The organic layer is separated. Then, it is dried through evaporation using sodium sulfate. Subsequently, the material is purified using silica gel chromatography and/or crystallization. Through out the entire specification of the present invention, all temperatures are expressed in degrees Celsius.

[0052]

Examples

Example 1a) 5-Methyl-2-(4-nitrophenyl)-2,4-dihydro-3-pyrazolone (Cyclization Reaction)

p-Nitrophenylhydrazine hydrochloride 1,63g and ethyl acetoacetate 1.26g were refluxed by heating in ethanol 30ml for 45 minutes. The mixture was slightly concentrated under reduced pressure. Isolated crystal was subsequently collected through suction filtration.

Obtained Material: 5-Methyl-2-(4-nitrophenyl)-2,4-dihydro-3-pyrazolone 1.20g (64% of the theoretical quantity)

Melting Point: 223 degrees Celsius

[0053]

Example 1b) 4-(2-Ethylphenylaminomethylene)-5-methyl-2-(4-nitrophenyl)-2,4-dihydro-3-pyrazolone (One Step Reaction Process: Addition of Formamide and Aniline)

5-Methyl-2-(4-nitrophenyl)-2,4-dihydro-3-pyrazolone 1g, 1,3,5-triazine 190mg and 2-ethylaniline 0.74ml were refluxed by heating in ethanol 50ml for four days. The solvent was evaporated under reduced pressure. The preliminary reaction product material obtained in this method was purified using chromatography with an eluent of a solvent mixture comprising dichloromethane and methanol, which were mixed at a ratio of 97:3.

Obtained Material: 4-(2-Ethylphenylaminomethylene)-5-methyl-2-(4-nitrophenyl)-2,4-dihydro-3-pyrazolone 1.33g (83% of the theoretical quantity)
Melting Point: 220 degrees Celsius

[0054]

Example 1c) 3-Methyl-4-aminomethylene-1-phenyl-4,5-dihydro-5-pyrazolone (Addition of Formamide)

1,3,5-triazine 8.11g (0.1mole) was added to a stirred suspension of 3-methyl-1-phenyl-5-phyrazolinone 52.3g (0.3mole) in ethanol 800ml. The mixture was refluxed while boiling for one hour. Subsequently, the solution was reduced to a small quantity through evaporation in a rotation evaporator. Crystal, which was isolated during this period, was cooled and then collected through suction filtration. Thus, the crystal 24.5 g was obtained. The obtained material was processed through chromatography using an eluent of a solvent mixture comprising dichloromethane and acetone with a ratio of 4:1, and 3-methyl-4-aminomethylene-1-phenyl-4,5-dihydro-5-pyrazolone was isolated. After evaporation from this source solution in a rotation evaporator, a resin-like material 36g was obtained. The resin-like material was processed by the same method of chromatography and a dimer compound (melting point: 180.6 degrees Celsius) 14.1g was obtained. This product material was re-crystallized in acetone.

[0055]

Example 1d) 3-Methyl-4-(2-propoxyphenylaminomethylene)-1-phenyl-4,5-dihydro-5-pyrazolone (Addition of Aniline)

3-Methyl-4-aminomethylene-1-phenyl-4,5-dihydro-5-pyrazolone 2g and 2-propoxyaniline trifluoroacetate 1.6g were added to ethanol. Subsequently, the solution was refluxed while boiling for 1.5 hours. The reaction solution was subsequently concentrated. Next, the reaction product material was isolated through chromatography using an eluent of a solvent mixture comprising methylbutylketone/hexane with a ratio of 4:1. Subsequently, the material was re-crystallized in a mixture of methylbutylketone/hexane.

Obtained Material: 3-Methyl-4-(2-propoxyphenylaminomethylene)-1-phenyl-4,5-dihydro-5-pyrazolone 1.5g (45.5% of the theoretical quantity). The dimer product material can not be detected.

[0056]

Example 1e) 4-(2-Methoxyphenylaminomethylene)-5-methyl-2-phenyl-2,4-dihydro-3-pyrazolone

5-Methyl-2-phenyl-2,4-dihydro-3-pyrazolone 2g, trimethylorthoformate 188ml and o-anisidine 1.29ml in glacial acetic acid 5ml were heated at 70 degrees Celsius for 2 hours as they were stirred. The reaction mixture was chilled and then methanol 10ml was added. Isolated precipitation was collected using suction filtration and subsequently, re-crystallized in ethyl acetate.

Obtained Material: 4-(2-Methoxyphenylaminomethylene)-5-methyl-2-phenyl-2,4-dihydro-3-pyrazolone 1.1g (31% of the theoretical quantity)
Melting Point: 143 degrees Celsius

[0057]

Example 2a: 4-(4,5-Dihydro-4-(2-ethylanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)-N-hexylbenzamide (Producing a Subsequent Derivative with 1-Substituent)

4-(4,5-Dihydro-4-(2-ethylanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid 0.5g, hexylamine 0.19ml (1.43 millimole) and DMF 20ml were mixed together in a reaction flask and stirred for 5 minutes at room temperature. Subsequently, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide HCl 0.27g (1.43 millimole), 1-hydroxybenzotriazole 0.19g (1.43 millimole) and N-

methylmorpholine 0.18ml (1.43 millimole) were successively added. Then, the mixture was stirred for three hours at room temperature. The completion of the reaction was confirmed using thin film chromatography (TLC in CH2CL2/MeOH, 9:1 (ninhydrin spray reagent).

[0058]

This reaction mixture was subsequently added to water 200ml (no precipitation), and then extraction was performed twice, using ethyl ether. The ether layer was collected and dried using sodium sulfate. Subsequently, filtration was performed and the ether was removed through evaporation under reduced pressure. The residuum, which was obtained in this method, underwent the finishing process using chromatography (column: silica gel Si60, eluent: methylbutyl ether).

Obtained Material: 4-(4,5-Dihydro-4-(2-ethylanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)-N-hexylbenzamide 250mg (41.6% of the theoretical quantity)

[0059]

Example 2b) 4-(2-Ethylanilinomethylene)-4,5-dihydro-3-methyl-1-(3-(1H-tetrazole-5-yl)phenyl)-1H-pyrazole-5-one (Producing a Subsequent Derivative with 1-Substituent)

3-(4,5-Dihydro-4-(2-ethylanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzonitrile 200mg (0.6 millimole) and toluene 20ml are mixed together. As it was stirred, the solution was refluxed by heating for 2 days. After the reaction period, a small amount of the source compound was still detected using chromatography. A finishing process was performed using the below method: The precipitation, which was produced during the reaction period, was collected using suction filtration. The material consisted of a material which was contaminated only with Sn salts. Accordingly, the material was purified using chromatography (column: silica gel Si60, eluent: CH_2Cl_2/MeOH, 9:1).

Obtained Material: 4-(2-Ethylanilinomethylene)-4,5-dihydro-3-methyl-1-(3-(1H-tetrazole-5-yl)phenyl)-1H-pyrazole-5-one 100mg (45.5% of the theoretical quantity)

[0060]

In addition to the compounds described in the production examples 1 and 2, specific 3-pyrazolone derivatives, which are expressed by the below formula I, were producing using the aforementioned method using triazine or trimethylorthoformate:

3 5-Methyl-2-(4-(4-morpholinylsulfonyl)phenyl)-2,4-dihydro-3-pyrazolone was produced from 4-(4-morpholinylsulfonyl)phenylhydrazine and ethyl acetoacetate. 4-(2-ethylanilinomethylene)-2,4-dihydro-5-methyl-2-(4-(4-morpholinylsulfonyl)phenyl)-3H-pyrazole-3-one was obtained from the above-produced material and 2-ethylaniline.

Melting Point: 275 degrees Celsius

[0061]

4 N-(3-(4,5-Dihydro-3-methyl-5-oxo-5H-pyrazole-1-yl)phenyl)acetoamide was produced from 3-acetoamidophenylhydrozine and ethyl acetoacetate. N-(3-(4-(2-Ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-5H-pyrazole-1-yl)phenyl)acetoamide was obtained from the above-produced material and 2-ethylaniline.

Melting Point: 263 degrees Celsius

[0062]

5 N,N-Diethyl-4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide was produced from N,N-diethyl-4-hydrazinobenzenesulfonamide and ethyl acetoacetate. N,N-Diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide was obtained from the above-produced material and 2-ethylaniline.

Melting Point 194 degrees Celsius

[0063]

6 N-Ethyl-4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide was produced N-ethyl-4-hydrazinobenzenesulfonamide and ethyl acetoacetate. N-Ethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide was obtained from the above-produced material and 2-ethylaniline.

Melting Point 260 degrees Celsius

[0064]

7 5-Methyl-2-(4-(4-morpholinylsulfonyl)phenyl)-2,4-dihydro-3-pyrazolone was produced from 4-(4-morpholinylsulfonyl)phenylhydrazine and ethyl acetoacetate. 4-(2-Butoxyanilinomethylene)-2,4-dihydro-5-methyl-2-(4-(4-morpholinylsulfonyl)phenyl)-3H-pyrazole-3-one was obtained from the above-produced material and 2-butoxyaniline.
Melting Point 171 degrees Celsius

[0065]

8 5-Methyl-2-(4-(4-morpholinylsulfonyl)phenyl)-2,4-dihydro-3-pyrazolone was produced from 4-(4-morpholinylsulfonyl)phenylhydrazine and ethyl acetoacetate. 4-(2-ethoxyanilinomethylene)-2,4-dihydro-5-methyl-2-(4-(4-morpholinylsulfonyl)phenyl)-3H-pyrazole-3-one was obtained from the above-produced material and 2-ethoxyaniline.
Melting Point 265 degrees Celsius

[0066]

9 5-Methyl-2-(4-(4-methyl-1-piperazinylsulfonyl)phenyl)-2,4-dihydro-3-pyrazolone was produced from 4-(4-methyl-1-piperazinylsulfonyl)phenylhydrazine and ethyl acetoacetate. 4-(2-ethylanilinomethylene)-2,4-dihydro-5-methyl-2-(4-(4-methyl-1-piperazinylsulfonyl)phenyl)-3H-pyrazole-3-one was obtained from the above-produced material and 2-ethylaniline.
Melting Point 254 degrees Celsius

[0067]

10a) 2-(3-Aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone (Hydrogen Addition of Substituent)

A solution of 5-methyl-2-(3-nitrophenyl)-2,4-dihydro-3-pyrazolone 15g in methanol 400ml underwent hydrogen addition under the presence of Raney nickel 10g. The catalyst was separated through filtration. The residuum, which was obtained after the solution was concentrated under reduced pressure, was re-crystallized in isopropanol.

Obtained Material: 2-(3-Aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone 8.0g (62% of the theoretical quantity)
Melting Point: 265 degrees Celsius

Similarly, the following compounds are obtained form corresponding nitro compounds: 2-(4-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone (amorphous): 2-(2-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone (amorphous).

[0068]

10b) Reaction of Amino Group, N Substituent of Pyrazole

Methanesulfonylchloride 2.2ml was added to a stirred solution of 2-(3-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone 4.0g in dichloromethane 30ml and pyridine 2ml, as it was being chilled with ice. Subsequently, the mixture was stirred for 2 hours. Then, the solution was washed in diluted hydrochloric acid and water, dried and subsequently, concentrated under reduced pressure. N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)methanesulfonamide was obtained from the above-produced N-(3-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)methanesulfonamide and 2-ethlyaniline.

Melting Point: 192 degrees Celsius

[0069]

11 Reaction of Amino Group, N Substituent of Pyrazole, with Methylchloroformate or Methanesulfonylchloride

Methylchloroformate 2.2ml was added to a stirred solution of 2-(3-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone 4.0g in dichloromethane 30ml and pyridine 2ml, as it was being chilled with ice. Subsequently, the mixture was stirred for 2 hours. Then, the solution was washed in diluted hydrochloric acid and water, dried and subsequently, concentrated under reduced pressure.

Obtained Materiel: Methyl N-(3-(4,5-Dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)carbamate 4.2g (76% of the theoretical quantity). Oily material

[0070]

This compound was reacted with 2-ethylaniline and methyl N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)carbamate, melting point, 229 degrees Celsius, was obtained. Similarly, N-(4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)methanesulfonamide was obtained from 2-(4-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone and methanesulfonylchloride. Moreover, methyl N-(4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)carbamate was obtained from 2-(4-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone and methylchloroformate.

[0071]

12 N-(4-(4,5-Dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)acetoamide (Reaction of Amino Group, N Substituent of Pyrazole, and Acetic Acid Derivative)

Acetic anhydride 1.0ml was added to 2-(4-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone 1.9g in tetrahydrofuran 40ml as it was being stirred and chilled with ice. Subsequently, the mixture was stirred for 2 hours. The solution was concentrated under reduced pressure. The residuum underwent the ordinary finishing process.

Obtained Material: N-(4-(4,5-Dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)acetoamide 1.5g (65% of the theoretical quantity). Oily material

[0072]

Similarly, N-(4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)trifluoroacetoamide was obtained from 2-(4-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone and trifluoroacetic anhydrate: N-(3-(4,5-Dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)trifluoroacetoamide was obtained from 2-(3-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone and trifluoroacetic anhydrate: N-(3-(4,5-Dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)acetoamide was obtained from 2-(3-aminophenyl)-5-methyl-2,4-dihydro-3-pyrazolone and acetic anhydrate:

[0073]

N-(4-(4,5-Dihydro-3-methyl-5-oxo-5H-pyrazole-1-yl)phenyl)acetoamide was obtained from 5-methyl-2-(4-aminophenyl)-2,4-dihydro-3-pyrazolone (which was obtained in the same manner as in Example 10) and acetic anhydrate. A subsequent reaction with 2-ethylaniline produced N-(4-(4-(2-

ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)acetoamide. Melting point: 230 degrees Celsius.

[0074]

13 N-(4-(4,5-Dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)-N-methylsulfonylmethanesulfonamide was obtained from 5-methyl-2-(4-aminophenyl)-2,4-dihydro-3-pyrazolone and methanesulfonylchloride. (This reaction was performed using a corresponding mole amount of methanesulfonylchloride in the same manner as in the production example 11.) The obtained material and 2-ethylaniline produced N-(4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)-N-methylsulfonylmethanesulfonamide. Melting point: 268 degrees Celsius.

[0075]

14 5-Methyl-2-(4-aminophenyl)-2,4-dihydro-3-pyrazolone and methanesulfonylchloride produced N-(4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)methanesulfonamide. (This reaction was performed in the same manner as in the production example 11.) The obtained material and 2-ethylaniline produced N-(2-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)methanesulfonamide. Melting point: 231 degrees Celsius.

[0076]

15 5-Methyl-2-(3-aminophenyl)-2,4-dihydro-3-pyrazolone and trifluoroacetic anhydrate produced N-(3-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)trifluoroacetoamide. (This reaction was performed in the same manner as in the production example 12.) The obtained material and 2-ethylaniline produced N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-5-yl)phenyl)trifluoroacetoamide. Melting point: 240 degrees Celsius.

[0077]

16 N,N-Diethyl-4-hydrazinobenzenesulfonamide and ethyl acetoacetate produced N,N-diethyl-4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. The obtained material and 2-ethoxyaniline produced N,N-diethyl-4-(4,5-dihydro-4-(2-ethoxyanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. Melting point: 170 degrees Celsius.

[0078]

17 N,N-Diethyl-4-hydrazinobenzenesulfonamide and ethyl acetoacetate produced N,N-diethyl-4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. The obtained material and 2-methoxyaniline produced N,N-diethyl-4-(4,5-dihydro-4-(2-methoxyanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. Melting point: 191 degrees Celsius.

[0079]

18 N-Ethyl-4-hydrazinobenzenesulfonamide and ethyl acetoacetate produced N-ethyl-4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. The obtained material and 2-ethoxyaniline produced 4-((2-ethoxyanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)-N-ethylbenzenesulfonamide. Melting point: 238 degrees Celsius.

[0080]

19 5-Methyl-2-(4-aminophenyl)-2,4-dihydro-3-pyrazolone and ethylchloroformate produced ethyl N-(4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)carbamate. (This reaction was performed in the same manner as in the production example 11.) The obtained material and 2-methoxyaniline produced ethyl N-(4-(4,5-dihydro-4-(2-methoxyanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)carbamate. Melting point: 212 degrees Celsius.

[0081]

20 5-Methyl-2-(4-aminophenyl)-2,4-dihydro-3-pyrazolone and propionylchloride produced ethyl N-(4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)propionamide. (This reaction was performed in the same manner as in the production example 11.) The obtained material and 2-ethoxyaniline produced N-(4-(4-(2-ethoxyanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)phenyl)propionamide. Melting point: 208 degrees Celsius.

[0082]

21 4-(1-Piperidylsulfonyl)phenylhydrazine and ethyl acetoacetate produced 5-methyl-2-(4-(1-piperidylsulfonyl)phenyl)-3H-pyrazole-3-one. The obtained material and 2-ethoxyaniline produced

4-(2-ethoxyanilinomethylene)-4,5-dihydro-5-methyl-2-(4-(1-piperidylsulfonyl)phenyl)-3H-pyrazole-3-one. Melting point: 252 degrees Celsius.

[0083]

22 N-tert-Butyl-4-hydrozinobenzenesulfonamide and ethyl butyrylacetate produced N-tert-butyl-4-(4,5-dihydro-3-propyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. The obtained material and 2-ethoxyaniline produced N-tert-butyl-4-(4-(2-ethoxyanilinomethylene)-4,5-dihydro-3-propyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. Melting point: 254 degrees Celsius.

[0084]

23 N-Acetyl-4-(4-(2-ethoxyanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide (Producing a N Substituent Derivative of Pyrazole after Condensing with an Aniline Derivative)

Acetic anhydride 0.17ml was dripped and added to a solution of 4-(4-(2-ethoxyanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide 1.0g and dimethylaminopyridine 0.9g in pyridine 30ml, as it was being chilled with ice. Subsequently, the mixture was stirred for 10 hours. The residuum, which was obtained after condensing under reduced pressure, was mixed with diluted hydrochloric acid. The isolated crystals were collected through suction filtration, and subsequently, was mixed with ethanol.

Obtained Material: N-Acetyl-4-(4-(2-ethoxyanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide 0.47g (42.5% of the theoretical quantity)
Melting Point: 282 degrees Celsius

[0085]

24 4-Hydrozinobenzenesulfonamide and ethyl acetoacetate produced 4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. The obtained material and 2-ethoxyaniline produced 4-(4-(2-ethoxyanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. Melting point: 241 degrees Celsius.

[0086]

25 Phenylhydrazine and methyl 5-hydroxy-3-oxo-pentanoate produced 5-(2-hydorxyethyl)-2-phenyl-2,4-dihydro-3-pyrazolone. The obtained material and 2-ethylaniline produced 4-(2-ethylanilinomethylene)-2,4-dihydro-5-(2-hydroxyethyl)-2-phenyl-1H-pyrazole-3-one.

[0087]

26 4-Methoxybenzylhydrazine and ethyl butyrylacetate produced 2,4-dihydro-2-(4-methyoxybenzyl)-5-propyl-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 4-(2-ethylanilinomethylene)-2,4-dihydro-2-(4-methyoxybenzyl)-5-propyl-3H-pyrazole-3-one. Oily material.

[0088]

27 2-Propoxybenzylhydrazine and ethyl butyrylacetate produced 2,4-dihydro-2-(2-propoxybenzyl)-5-propyl-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 4-(2-ethylanilinomethylene)-2,4-dihydro-2-(2-propoxybenzyl)-5-propyl-3H-pyrazole-3-one. Melting point: 75.2 degrees Celsius.

[0089]

28 4-Bromophenylhydrazine and ethyl butyrylacetate produced 2-(4-bromophenyl)-2,4-dihydro-5-propyl-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 2-(4-bromophenyl)-4-(2-ethylanilinomethylene)-2,4-dihydro-5-propyl-3H-pyrazole-3-one. Melting point: 126.9 degrees Celsius.

[0090]

29 4-Nitrophenylhydrazine and ethyl butyrylacetate produced 2,4-dihydro-2-(4-nitrophenyl)-5-propyl-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 4-(2-ethylanilinomethylene)-2,4-dihydro-2-(4-nitrophenyl)-5-propyl-3H-pyrazole-3-one. Melting point: 211 degrees Celsius.

[0091]

30 3-Hydrazinobenzenesulfonic acid and ethyl butyrylacetate produced 3-(4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzenesulfonic acid. The obtained material and 2-ethylaniline

produced 3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzenesulfonic acid. Melting point: 258.6 degrees Celsius.

[0092]

31 4-Hydrazinobenzenesulfonic acid and ethyl butyrylacetate produced 4-(4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzenesulfonic acid. The obtained material and 2-ethylaniline produced 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzenesulfonic acid. Melting point: 205.2 degrees Celsius.

[0093]

32 4-Nitrophenylhydrazine and diethyl 3-oxoglutarate produced ethyl 2-(4,5-dihydro-1-(4-nitrophenyl)-5-oxo-1H-pyrazole-3-yl)acetate. The obtained material and 2-ethylaniline produced 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-nitrophenyl)-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 224.5 degrees Celsius.

[0094]

33 4-Hydrazinobenzoic acid and ethyl acetoacetate produced ethyl 4-(4,5-dihydro-5-oxo-3-methyl-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-ethylaniline produced 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-methyl-1H-pyrazole-1-yl)benzoic acid. Melting point: 291 degrees Celsius.

[0095]

34 2-Pyridylhydrazine and ethyl butyrylacetate produced ethyl 2,4-dihydro-2-(2-pyridyl)-5-propyl-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 4-(2-ethylanilinomethylene)-2,4-dihydro-2-(2-pyridyl)-5-propyl-3H-pyrazole-3-one. Melting point: 151 degrees Celsius.

[0096]

35 2-Pyridylhydrazine and ethyl acetoacetate produced ethyl 2,4-dihydro-5-methyl-2-(2-pyridyl)-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 4-(2-

ethylanilinomethylene)-2,4-dihydro-5-methyl-2-(2-pyridyl)-3H-pyrazole-3-one. Melting point: 182.9 degrees Celsius.

[0097]

36 4-Hydrazinobenzoic acid and ethyl butyrylacetate produced ethyl 4-(4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-ethylaniline produced 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid. Melting point: 254.5 degrees Celsius.

[0098]

37 4-(4-(2-Ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid and hexylamine produced 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)hexylbenzamide. Melting point: 62.1 degrees Celsius.

[0099]

38 4-(4-(2-Ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid and aqueous ammonia produced 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzamide. Melting point: 225.2 degrees Celsius.

[0100]

39 4-(4-(2-Ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid and an aqueous solution of N,N-diethylamine produced N,N-diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzamide. Melting point: 112 degrees Celsius.

[0101]

40 4-Pyridylhydrazine and ethyl butyrylacetate produced 2,4-dihydro-5-propyl-2-(4-pyridyl)-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 4-(2-ethylanilinomethylene)-2,4-dihydro-5-propyl-2-(4-pyridyl)-3H-pyrazole-3-one. Melting point: 159.2 degrees Celsius.

[0102]

41 4-Chlorophenylhydrazine and ethyl acetoacetate produced 2-(4-chlorophenyl)-2,4-dihydro-5-methyl-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 2-(4-chlorophenyl)-4-(2-ethylanilinomethylene)-2,4-dihydro-5-methyl-3H-pyrazole-3-one.

[0103]

42 4-(4-(2-Ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid and an aqueous solution of diethylamine produced N,N-diethyl-4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzamide. Melting point: 123 degrees Celsius.

[0104]

43 4-(4-(2-Ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid and hexylamine produced 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)-N-hexylbenzamide. Melting point: 46.7 degrees Celsius.

[0105]

44 4-(4-(2-Ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid and aqueous ammonia produced 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzamide. Melting point: 170 degrees Celsius.

[0106]

45 4-Hydrazinobenzonitrile and ethyl butyrylacetate produced 4-(4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzonitrile. The obtained material and 2-ethylaniline produced 4-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzonitrile. Melting point: 196.7 degrees Celsius.

[0107]

46 N,N-Diethyl-3-hydrazino-4-methoxybenzenesulfonamide and ethyl butyrylacetate produced N,N-diethyl-3-(4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)-4-methoxybenzenesulfonamide. The obtained material and 2-ethylaniline produced N,N-diethyl-3-(4-(2-

ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)-4-methoxybenzenesulfonamide. Oily material.

[0108]

47 3-Hydrazinobenzonitrile and ethyl acetoacetate produced 3-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzonitrile. The obtained material and 2-ethylaniline produced 3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzonitrile. Melting point: 210.8 degrees Celsius.

[0109]

48 N-Hexyl-3-hydrazino-4-propoxybenzenesulfonamide and ethyl acetoacetate produced 3-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-ylmethyl)-N-hexyl-4-propoxybenzenesulfonamide. The obtained material and 2-ethylaniline produced 3-(4-(2-ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-ylmethyl)-N-hexyl-4-propoxybenzenesulfonamide. A resin-like material.

[0110]

49 2-Hydrazinobenzoic acid and ethyl butyrylacetate produced 2-(4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-ethylaniline produced 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzoic acid. Melting point: 126.9 degrees Celsius.

[0111]

50 4-(4-(2-Ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)benzonitrile and trimethyl-tin-azide produced 4-(2-ethylanilinomethylene)-2,4-dihydro-5-propyl-2-(4-(1H-tetrazole-5-yl)phenyl-3H-pyrazole-3-one. Melting point: 248.5 degrees Celsius.

[0112]

51 3-Pyridylhydrazine and ethyl butyrylacetate produced 2,4-dihydro-5-propyl-2-(3-pyridyl)-3H-pyrazole-3-one. The obtained material and 2-ethylaniline produced 4-(2-

ethylanilinomethylene)-2,4-dihydro-5-propyl-2-(3-pyridyl)-3H-pyrazole-3-one. Melting point: 143.9 degrees Celsius.

[0113]

52 3-(4-(2-Ethylanilinomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzonitrile and trimethyl-tin-azide produced 4-(2-ethylanilinomethylene)-2,4-dihydro-5-methyl-2-(3-(1H-tetrazole-5-yl)phenyl-3H-pyrazole-3-one. Melting point: 261.6 degrees Celsius.

[0114]

53 Hydrazinobenzoic acid and ethyl acetoacetate produced 4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-trifluoromethylaniline produced 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-trifluoromethylanilinomethylene)-1H-pyrazole-1-yl)benzoic acid. Melting point: 289.4 degrees Celsius.

[0115]

54 p-Hydrazinobenzoic acid and diethyl 3-oxoglutarate produced 4-(3-ethoxycarbonylmethyl-4,5-dihydro-5-oxo-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-trifluoromethylaniline produced 4-(4-(2-ethylanilinomethylene)-3-ethoxycarbonylmethyl-4,5-dihydro-5-oxo-1H-pyrazole-1-yl)benzoic acid. Melting point: 246 degrees Celsius.

[0116]

55 p-Hydrazinobenzoic acid and ethyl acetoacetate produced 4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-(2-propionyloxy)aniline produced 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-(2-propionyloxy)anilinomethylene)-1H-pyrazole-1-yl)benzoic acid. Melting point: 267.9 degrees Celsius.

[0117]

56 p-Hydrazinobenzoic acid and ethyl acetoacetate produced 4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-propoxyaniline produced 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-propoxyanilinomethylene)-1H-pyrazole-1-yl)benzoic acid. Melting point: 259.6 degrees Celsius.

[0118]

57 p-Hydrazinobenzoic acid and ethyl acetoacetate produced 4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-(2-propenyloxy)aniline produced 4-(4,5-dihydro-3-methyl-5-oxo-4-(2-(2-propenyloxy)anilinomethylene)-1H-pyrazole-1-yl)benzoic acid. Melting point: 240.4 degrees Celsius.

[0119]

58 p-Hydrazinobenzoic acid and ethyl acetoacetate produced 4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-methoxyaniline produced 4-(4,5-dihydro-4-(2-methoxyanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid. Melting point: > 300 degrees Celsius.

[0120]

59 p-Hydrazinobenzoic acid and ethyl acetoacetate produced 4-(4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid. The obtained material and 2-isopropylaniline produced 4-(4,5-dihydro-4-(2-isopropylanilinomethylene)-3-methyl-5-oxo-1H-pyrazole-1-yl)benzoic acid. Melting point: 269.5 degrees Celsius.

[0121]

60 3-(4,5-Dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide (this compound can be purchased) and 2-ethylaniline produced 3-(4-(2-ethylanilinomethyleneaminomethylene)-4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-1-yl)benzenesulfonamide. Melting point: 229.2 degrees Celsius.

[0122]

61 Ethyl 2-(1-(4-aminophenyl)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate and trifluoroacetic anhydride were reacted. A subsequent reaction was performed with 2-ethylaniline and ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-trifluoroacetoamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 197 degrees Celsius.

[0123]

62 Ethyl 2-(1-(4-aminophenyl)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate and methylchloroformate were reacted. A subsequent reaction was performed with 2-ethylaniline and ethyl 2-(1-(4-methoxycarbonylaminophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 145 degrees Celsius.

[0124]

63 Ethyl 2-(4,5-dihydro-1-(4-aminophenyl)-5-oxo-1H-pyrazole-3-yl)acetate and methanesulfonylchloride were reacted. A subsequent reaction was performed with 2-ethylaniline and ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methanesulfonamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 165 degrees Celsius.

[0125]

64 Ethyl 2-(4,5-dihydro-1-(4-aminophenyl)-5-oxo-1H-pyrazole-3-yl)acetate and acetylchloride were reacted. A subsequent reaction was performed with 2-ethylaniline and ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 197 degrees Celsius.

[0126]

In addition, the compounds below were produced: Ethyl 2-(1-(4-N,N-diethylsulfamoyl)phenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 146 degrees Celsius. Ethyl 2-(1-(4-N,N-diethylsulfamoyl)phenyl)-4-(2-ethoxyanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 127 degrees Celsius. Ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 194 degrees Celsius.

[0127]

Ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1-(4-trifluoroacetoamidophenyl)-1H-pyrazole-3-yl)acetate. Melting point: 197 degrees Celsius. Ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methoxycarbonylaminophenyl)-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 144

degrees Celsius. Ethyl 2-(4-(2-ethylanilinomethylene)-4,5-dihydro-1-(4-methanesulfonamidophenyl)-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 165 degrees Celsius.

[0128]

Ethyl 2-(1-(4-acetoamidophenyl)-4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-1H-pyrazole-3-yl)acetate. Melting point: 168 degrees Celsius. 2-(4-(2-Ethylanilinomethylene)-4,5-dihydro-1-(4-methoxycarbonylaminophenyl)-5-oxo-1H-pyrazole-3-yl)acetic acid. Melting point: 181 degrees Celsius. N-(3-(4-(2-Ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)methanesulfonamide. Melting point: 214 degrees Celsius.

[0129]

N-(3-(4-(2-Ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)acetoamide. Melting point: 181 degrees Celsius. Methyl N-(3-(4-(2-ethylanilinomethylene)-4,5-dihydro-5-oxo-3-propyl-1H-pyrazole-1-yl)phenyl)carbamate. Melting point: 203 degrees Celsius. Ethyl 2-(4-(2-Ethylanilinomethylene)-4,5-dihydro-5-oxo-1-(3-trifluoroacetoamidophenyl)-1H-pyrazole-1-yl)acetate. Melting point: 174 degrees Celsius.

[0130]

The examples below pertain to pharmaceuticals.

Example A: Injection Vials

A solution included an active material, which was expressed by formula I, 100g and disodium hydrogenphosphate 5g in double distilled water 3 liter. The pH of the solution was adjusted to 6.5 using 2N hydrochloric acid. Then, the solution was sterilized, filtered and placed in injection vials. Subsequently, the solution was freeze-dried under sterilized conditions. These vials were then sealed under sterilized conditions. Each injection vial contained 5mg of the active material.

Example B: Suppository

A mixture of an active material, which was expressed by formula I, 20g, soya lecithin 100g, and cacao butter 1,400g were melted, placed in a mold and cooled. Each piece of the suppository contained 20mg of the active material.

[0131]

Example C: Solution

A solution was prepared with an active material, which was expressed by formula I, 1g, $NaH_2PO_4 \bullet 2H_2O$ 9.38g, $Na_2HPO_4 \bullet 12H_2O$ 28.48g, and benzalconiumchloride 0.1g in double distilled water 940ml. The pH of the solution was adjusted to 6.8 and the total volume was made to be 1 liter. Subsequently, the solution was irradiated for sterilization. This solution can be used in a form of eye drops.

Example D: Ointment

An active material, which was expressed by formula I, 500mg was mixed with petrolatum 99.5g under sterilized conditions.

[0132]

Example E: Tablets

A mixture of an active material, which was expressed by formula I, 1kg, lactose 4kg, potato starch 1.2kg, talc 0.2kg and magnesium stearate 0.1kg was compressed using a conventional method and tablets were prepared. Each tablet contained 10mg of the active material.

Example F: Coated Tablets

Tablets were formed by compression as described in Example E. Subsequently, using a conventional method, they were coated with a coating film, comprising sucrose, potato starch, talc, tragacanth rubber and a colorant.

[0133]

Example G: Capsules

An active material, which was expressed by formula I, 20kg was filled in hard gelatin capsules using a conventional method. Each capsule contained 20mg of the active material.

Example H: Ampoules

A solution of an active material, which was expressed by formula I, 1kg in double distilled water 60 liters was sterilized, filtered and placed in ampoules. The solution was freeze-dried under sterilized conditions. Subsequently, the ampoules were sealed under sterilized conditions. Each ampoule contained 10mg of the active material.

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(71) Applicant: 591032596
250 Frankfurter Strasse
D-64293, Darmstadt
Federal Republic of Germany

(72) Inventor: Michael Aldt
250 Frankfurter Strasse
D-64293, Darmstadt
Federal Republic of Germany

(72) Inventor: Rofuss Yonass
250 Frankfurter Strasse
D-64293, Darmstadt
Federal Republic of Germany

(72) Inventor: Maria Kristadlar
250 Frankfurter Strasse
D-64293, Darmstadt
Federal Republic of Germany

(72) Inventor: Gunntar Schnaider
250 Frankfurter Strasse
D-64293, Darmstadt
Federal Republic of Germany

(72) Inventor: Michael Krokou
250 Frankfurter Strasse
D-64293, Darmstadt
Federal Republic of Germany